REMARKS

After the entry of the present amendment, Claims 85-92 and 107-118 are pending. Claims 85, 87, 90, 92, 107, 109, 110-112, and 116-118 have been amended. Support for the amendments can be found in the specification and original claims, for example Claims 1, 11, and 12 and paragraphs **0130, 0032,** and **0139** (of the online USPTO publication). No new matter has been added by these amendments.

Applicants thank the Examiner for acknowledging the withdrawal of the rejections of Claims 85-92 and 114-115 under 35 U.S.C. §112; Claims 85, 87-90, 92, and 109-115 under 35 U.S.C. §103(a); and Claims 85-92 and 109-118 under 35 U.S.C. §103(a).

Claims 85-92, 107-109, 111, and 118 are adequately definite

The Examiner has asserted that Claims 85, 90, 107, 111, and 118 are unclear because it is allegedly unclear which "result" is being output. Applicants have amended Claims 85, 90, 107, 111, and 118 to explicitly note what is being output. As such, Applicants submit that the Claims are adequately definite and request that the rejections be withdrawn and the claims allowed.

Applicants note that while Claim 109 was listed in the first part of the rejection on page 3 of the Office Action, it was not then subsequently rejected. As Claim 109 does note what is being output, Applicants assume that the claim was not intended to be rejected in the Office Action. If this is incorrect, Applicants request further clarification of the rejection.

Amended Claims 85-92, 107-109, 111, and 118 are Directed to Statutory Subject Matter.

The Examiner has asserted that Claims 85-92, 107-109, 111, and 118 are not directed to statutory subject matter. While Applicants do not necessarily agree, Applicants have amended the claims in a manner consistent with the suggestions made by the Examiner on page 5 of the Office Action. These claims now recite that the relevant information is output "to a user or a memory." As such, Applicants submit that the claimed inventions are clearly directed to statutory subject matter.

Furthermore, as the Examiner's rejection appears to be based upon the §112 issue noted above (see page 5 of the Office Action), and as the §112 issue has been resolved by the above noted amendments, Applicants note that the recitation of the specific type of result to be output

-11-

also addresses the Examiner's rejection. Applicants request that the rejections be withdrawn and the claims allowed.

Claims 85-92 and 109-118 are Nonobvious over Rognan in View of Welch

        The Examiner has rejected Claims 85-92 and 109-118 as obvious in light of Rognan and Welch. Applicants respectfully traverse the rejection. The claims, as presently amended, include elements that are not taught in either Rognan or Welch (or in their combination as proposed by the Examiner). As not all of the elements have been taught, a *prima facie* case of obviousness has not been established. In addition, Applicants note that when the actual teachings of Rognan are considered, there is no reason for one of skill in the art would not have had a reason to combine the references, in the manner suggested by the Examiner.

<u>Not all of the Claimed Elements are Taught by the References</u>
The Scaling of Binding Affinities is Not Taught in the Cited References

        The Examiner has asserted that Rognan teaches "normalization (*i.e.* scaling) of data values between 0 and 1 [FIG. 4]." (Office Action, page 6). While FIG. 4 may actually display "values" that are between 1 and 0, Applicants note that these are *not* scaled binding affinities. Rather, the graph in Rognan is a chart showing the influence of the terms on the <u>predictivity</u> for various combinations of components for the model (see legend). It is clear that the actual binding affinities themselves are not being scored between 1 and 0, as the graph is a measure of the "influence of the regression terms on the predictivity of the... model" and thus is not a normalization of the free energies or affinities of the various terms. As such, Rognan does not teach the element of "scaling said first binding affinity."

        In addition, the teachings of Welch do not provide this missing element. In the rejection, the Examiner has noted Table 3 of Welch as providing "averaged" scoring values of less than 1. However, the values in Table 3 are actually greater than 1 across the various control proteins, and thus are clearly not being scaled between 0 and 1. In addition, Table 3 is directed to the performance of Welch's tool on various positive controls, and is generally inapplicable to the scaling of a final predicted binding affinity. As such, not all of the elements have been taught by the cited references and a *prima facie* case of obviousness has not been established.

Neither Rognan nor Welch Teach Determining a First and Second Binding Affinity

In the Office Action, the Examiner has asserted that Rognan "teaches a plurality of predictive methods," and thus teaches a first affinity and a second affinity as recited in the claims. Applicants respectfully disagree as the terms are applied to the instant claims.

Rognan does not teach the use of a plurality of methods for predicting numerous different binding affinities; rather, Rognan teaches a <u>single</u> predictive method that involves numerous <u>components</u> (H-binding, rotational, buried-polar, desolvation scores, etc.) to obtain a <u>single</u> prediction of free energy (see the bottom of FIG. 1). Applicants note that the separate <u>components</u> of free energy being combined in Rognan (FIG. 1, H-bond, etc.) cannot be equated with separate predictive methods for determining binding affinities, as each of the values in Rognan, on their own, is not an actual prediction of the affinity between the peptide and protein.[1] As it is clear that Rognan must sum these values (as shown in FIG. 1) to obtain a free energy prediction between the protein and the peptide, it is clear that these values cannot be considered to represent a first and second affinity, as recited in the claims.[2]

To clarify this distinction, Claim 85 has been further amended to note that the first and second affinities are "binding affinities," and that the binding affinities "represent the likelihood that a peptide will bind with a protein." The other independent claims have been similarly amended. Applicants note that the individual components that contribute to Rognan's calculation in FIG. 1 cannot be considered to be binding affinities as they, individually, do not represent the likelihood that a peptide will bind to a protein. Instead, Rognan's values only provide the energetic contribution of one (H bonds, etc), where multiple components are <u>required</u> to obtain the prediction.

Given this amendment, it should be clear that subparts or components that must be summed in Rognan to obtain a single affinity are not relevant to the elements that are presently recited in the claims. As such, it is clear that the subparts taught in Rognan (FIG. 1) do not teach

---

[1]   If they were an accurate prediction of the affinity, then Rognan would only use one such value to determine the free energy of the interaction between the peptide and protein.

[2]   For clarification, Applicants note that the presently claimed methods (if applied to Rognan's technique) would involve taking the <u>actual</u> prediction produced by Rognan (the bottom of FIG. 1), scaling that value accordingly, and then combining with a <u>different predictive method</u>.

or suggest the recited steps of determining a first binding affinity and a second binding affinity (each of which separately represents the likelihood that a peptide would associate with a protein), much less scaling and combining the results as claimed. As such, it is clear that these elements have not been taught by the cited references and a *prima facie* case of obviousness has not been established.

Combining Scaled Binding Affinities are Not Taught in the Cited References.

In addition, even if FIG. 4 taught scaling (and as discussed above, Applicants believe it does not), Rognan does not teach that the scaled values in FIG. 4 are to be combined. Applicants note that FIG. 4 of Rognan is not part of the calculation or summing that occurs in FIG. 1, rather as noted above, FIG. 4 represents an analysis of the "influence of the regression terms on the predictivity of the …training model…" Thus, one of skill in the art would not read Rognan as teaching that one should combine the values in FIG. 4 of Rognan, as doing so would be meaningless given the actual teachings in Rognan. Moreover, as FIG. 4 is not actually addressing scaled binding affinities as recited in the claims, even if one did combine these values, as suggested in the Office Action, one would not obtain the presently claimed combination.

Applicants acknowledge that Rognan does teach combining various components that can be summed to get a complete free energy estimation (or more precisely, a "prediction of ΔG_{bind}" in FIG. 1). However, Rognan is not suggesting that the scaled values in FIG. 4, somehow be used in FIG. 1 of Rognan. Rather, the data in FIG. 4 of Rognan was used to observe/determine the "best combination" of the various interactions (see columns 1 and 2 of page 4654 and the legend). Thus, it is clear that Rognan does not teach these recited elements.

Applicants note that Welch does not teach these elements either. As such, it is clear that a *prima facie* case of obviousness has not been established.

On a more general note, Applicants note that the summing of the components in Rognan cannot, scientifically, be considered the same as the combination that is occurring in the claimed methods. In particular, the summing in Rognan is occurring because the full free energy of the interaction being modeled in Rognan involves each of the disclosed components (H-bonds etc., see Rognan generally). Thus, to obtain the full ΔG_{bind} all of the components should be summed as shown in FIG. 1. In contrast, the presently recited method is taking the novel and nonobvious

approach of combining finally predicted, scaled, binding affinities, in a specific manner, so that useful information regarding the interaction between the protein and peptide (or epitope) can be determined. Simply put, the logic behind the combination in Rognan is not applicable to the combination recited in the recited claims.

There is no Reason to make Examiner's Proposed Combination

Finally, the Examiner has asserted that one of skill in the art would have been motivated to combine the predictive method taught by Welch with Rognan, since Rognan "suggest[ed] combining different predictive methods for determining binding affinity [FIG. 1 and p. 4644, Col. 1, paragraph 3]." Applicants respectfully disagree with the Examiner's characterization of Rognan.[3]

In regard to the teachings of Rognan in general and FIG. 1 in particular, as explained above, Rognan is directed to combining components of a single free energy calculation to get a single free energy prediction (or ΔG_{bind} in particular). These components are things such as H bonds, lipophilic interactions, rotational, buried polar scores and desolvation scores. As will be appreciated by one of skill in art, each of these contribute to a single total value that Rognan is determining; they do not each separately represent a separate prediction of binding affinity, as recited in the present claims. As such, Rognan does not suggest that one would want to combine various methods for predicting binding affinities as suggested by the Examiner. As such, Applicants submit that one of skill in the art would not have combined or modified Rognan as proposed by the Examiner.

Claims 107 and 108 are Nonobvious

As Claims 107 and 108 were not rejected as obvious in light of Rognan and Welch, Applicants assume that the Claims, as amended to overcome the rejections under 35 U.S.C. §101 and §112, are acknowledged to be nonobvious over the cited art. If this is incorrect, Applicants

---

[3] Applicants note that there is no page "4644" in Rognan, as cited in the Office Action at page 7. If there was something specific that the Examiner was referring to with this citation, Applicants request further clarification on the record.

request that the rejection of the claims be made of record so that Applicants can address any concerns that the Examiner might have.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.
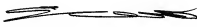
CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and request the same. If, however, some issue remains that the Examiner feels can be addressed by Examiner Amendment, the Examiner is cordially invited to call the undersigned for authorization.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/8/08

By: _____
Eli A. Loots
Registration No. 54,715
Attorney of Record
Customer No. 20995
(415) 954-4114

5057755/032408

-16-